REMARKS

Claims 198-325 are in this application. Claims 198-325 replace Claims 59-197.

The Examiner has rejected Claims 59-197 under 35 USC 112, second paragraph. Applicants respectfully traverse this rejection.

The Examiner states that Claims 59-197 are ambiguous as it appears that in the definition of R_7 one of these rings is missing the terminal part. The Examiner's attention is drawn to the disclosure in original Claim 1 and the corresponding disclosure in the specification on page 12 where it states that the R_7 moiety is linked either to two core molecules of the formula I to form a bis compound or the R_7 moiety has one of its linked bonds linked to the core of formula I and the second of its linked bonds is linked to a phenyl carboxylic acid or ester moiety thereof. Therefore both of the bonds of the cyclic R_7 are accounted for. This is not meant that R_7 together with R_5 or R_6 make these spiro compounds. This group links two of the structures of the formula I so that there would be one R_7 group between two of the core molecules. In Claim 198 and the other claims defining the structure of formula I now provide that the R_7 moiety is linked to 2 core molecules of the formula I to form a bis compound. Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner states that the claims are anticipated by or obvious over a number of references which will be discussed in more detail below. It must be noted that although the compounds defined in the claims appear similar in structure to known antibacterial quinolones, they are relatively inactive bacterially (cf. below) and now for the first time are shown to be effective efflux pump inhibitors (hereinafter "EPIs.").

The Examiner's argument that because compounds are active against resistant microbial strains, they are inherently also EPIs is not correct. Attached is an article (Attachment 1) "Bacterial active efflux pumps: a lifestyle" from the Newsletter of the International Society of Chemotherapy, April 2003, volume 7, number 1 which describes and clearly points out the function of efflux systems and the differentials of antibiotics to serve as substrates for different efflux pumps (cf. column 1 of attachment on page 3). This passage while mentioning some compound classes which are under investigation, does not include the fluoroquinolone class which is being claimed in this application as having EPI activity. The section "Future Developments" highlights the efforts underway to find novel efflux pump inhibitors.

As shown below, compounds may have antibacterial activity, EPI activity or both:

	Has Antibacterial Activity	Has EPI Activity
Case 1	Yes	No or low activity
Case 2	Yes	Yes
Case 3	No or low activity	Yes

The testing methods that have used are known for measuring EPI activity and have enabled the identification of EPI compounds which fall under all the Cases. For cases 2 and 3, in the tables 1 - 4 in the specification, the values for the FIC index or for the differences in zone size indicate the range of the potency of the EPIs for the different efflux pump bearing strains used and the antibacterial compound known to be a good substrate for the efflux pump of the respective strains.

At this time, the independent claims have been amended to define the EPIs as those which have no or low activity and have EPI activity. This data is shown in Attachment 2. Attachment 3 includes a table showing the MIC rank order values of different clinically developed fluoroquinolones with the efflux pump-bearing strain S. aureus 1199 B. The data indicate that besides efflux, other mechanisms also operate to raise the MIC levels of the compound against the resistant strains.

The Examiner has rejected Claims 59-197 under 35 USC 102 (e) as anticipated by or in the alternative under 35 USC 103 (a) as obvious over Ledoussal (U.S. Patent 6,329,391). Applicants respectfully traverse this rejection.

Ledoussal acknowledges in the '391 patent in column 3, lines 5 – 21 that "pathogenic bacteria are known to acquire resistance via several distinct mechanisms....". Although the object of the invention is to find quinolones that can be used against resistant microbes, Ledoussal has not specifically stated EPI activity as an intrinsic property of their compounds. Essentially, Ledoussal's molecules are NON-FLUORINATED-QUINOLONES (NFQs) which are said to "defy the art-accepted structure/activity relationships (column 3, lines 37 – 39). These NFQs are distinctly different from the compounds. As amended, all of the compounds included in the claims bear a 6-fluorine substituent in the fluoroquinolone core. Ledoussal provides no detailed biological activity of their compounds, except in a very general statement of ".... certain compounds ..... have MIC values ..... upto about 500 times lower than ciprofloxacin..." (column 19, lines 59 - 60).

To show, as the Examiner would like, that the compounds of Ledoussal are not efflux pump inhibitors, recourse has to be had to other publications of Ledoussal et al., which elaborate on the compounds described in '391. Such publications are posters from Ledoussal on NFQs presented at ICAAC conferences in 2001. See attachment 4. . It is clear from various statements made in the different abstracts that the object of the discovery programmes was to identify inhibitors of type II bacterial topoisomerases (e.g. DNA gyrase) via different methodologies, modelling and algorithms. None of these techniques was specifically oriented, as is the present application, to identify efflux pump inhibitors. Ledoussal's posters also describe the relationship between the bacterially inhibitory topoisomerase inhibition and the reduction in human topoisomerase inhibition. In these NFQs, a contribution of the 7-position side chain is supported by small molecule modelling and an algorithm enabling the design of potent broad spectrum agents. Again no specific mention of EPI activity is in evidence. The compounds included in the MIC tables of the R_7 substituent in the NFQs are not compounds with substituents which are listed in the tables in the specification and are claimed as EPIs.

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. In re Paulsen, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. Scripps Clinic & Res. Found. v. Genentech, Inc., 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). For the reasons described above Ledoussal does not include each and every element of the claimed invention and thus cannot anticipate the claimed invention.

In additional, Ledoussal does not make obvious the claimed invention. According to MPEP 2141 when applying 35 USC 103, the following tenets of patent law must be adhered to:

> (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and (D) reasonable expectation of success is the standard with which obviousness is determined.

In making this rejection, the Examiner is relying on impermissible hindsight.

A reference must be considered for what it would teach someone skilled in the art at the time the invention was made and not be applied based on "hindsight". See Panduit Corp. V. Dennison Manufacturing Co. 227 USPQ 337, 343 (Fed. Cir. 1985):

> It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art.

In making its obviousness determination, a court must view the prior art without reading into that art the patent's teachings. Vandenberg v. Dairy Equipment, 224 U.S.P.Q. 195 (Fed. Cir. 1987) citing In re Sponnoble, 160 U.S.P.Q. 237 (CCPA 1969). In Uniroyal . Rudkin-Wiley, 50 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988) the CAFC stated:

> The obviousness standard, while easy to expound, is sometimes difficult to apply. It requires the decision maker to return to the time the invention was made. The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time...That which may be clear and thus obvious to a court, with the invention fully diagramed and aided by experts in the field, may have been a breakthrough of substantial dimension when first unveiled [citations omitted]. In this case we are convinced that the district court misapplied the obviousness standard. It has impermissibly used hindsight to reconstruct the claimed invention from prior art with the invention before it and aided by Uniroyal's expert, rather than viewing the invention from the position of a person of ordinary skill at the time it was made. When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.

Therefore, for the reasons explained above Ledoussal does not anticipate nor make obvious the claimed invention and it is respectfully requested that the rejection be withdrawn.

The Examiner has rejected Claims 59-167 as being anticipated by or being obvious in view of Ito. Applicants respectfully traverse this rejection.

Ito states in column 2, lines 13 – 32 the "contrariness to general predictability of their compounds", which now have "potent antibacterial activities and are highly safe with reduced adverse reactions such as phototoxicity, induction of chromosomal aberration and

induction of convulsion". Ito's compounds are not stated to be EPIs. Additionally, Ito (column 13, lines 35-36) teaches ".....as an active ingredient, at least one substance selected from the group ..... upto line 44..... as an antibacterial agent". This teaching does not convey use of a compound outside the stated group of Ito's compounds which are distinct from the compounds of this invention. For the reasons explained above a compound that is devoid of or has low antibacterial activity can be used as an EPI, the method to treat microbial infections by use of an antimicrobial agent and an efflux pump inhibitor as defined in the claims is not disclosed or suggested by Ito.

The Examiner cites Ito's description in column 24, lines 65-67 of '026, "..., induce no.... chromosomal aberration, and induction of convulsion, ...". The Examiner is to be referred to column 23, lines 33 – 36. No actual values of the incidence rates of the aberration cells are provided for a negative control in the experimental procedure, together with actual values for the tested and reference compounds. It is known that the incidence rate of aberration occurring spontaneously in a normal cell population is around 1 – 4 %. Therefore, occurrence of an incidence rate of aberration above 6 – 7 % is itself quite abnormal. Additionally, for the reference compound A, viz. ciprolfoxacin, also no actual values of the incidence rate of aberration is provided. Literature values for ciprofloxacin are reported to be ca. 6% (cf. references enclosed (Attachment 5). The fact that different cells were used, CHL in '026 versus HPL in the enclosed abstract, makes no difference to the percentage values obtained in in-vitro tests. Different dosages are also used in the two described methods. In the absence of exact values, no conclusion can be arrived at about the genosafety of the test compounds or the reference compounds). An approximate statement like the one made by Ito in '026 viz. ".... less than 10% ..." cannot be taken by one skilled in the art as evidence that the compounds of '026 do not induce chromosomal aberration.

In '026, the Examiner is also to be referred to the section on "The induction of convulsions"(column 23, item 4) and in particular to column 24, lines 28 – 46 and TABLE 2, lines 50 – 60. The respective doses of the test compounds and the reference compounds A and B which were intracerebroventricularly administered are not stated. In the absence of such information, the results in TABLE 2 under the column "i.c.v." are meaningless to one skilled in the art.

Therefore, it is respectfully requested that the rejection be withdrawn.

The Examiner has rejected Claims 59-197 under 35 USC 102 (b) as anticipated by or in the alternative under 35 USC 103 (a) as obvious over Miyake (U.S. Patent 5,889,009).

Applicants respectfully traverse this rejection.

Applicants have provided evidence for the first time that fluoroquinolone compounds with structural features in certain combinations, as defined in the formula, have EPI activity, but have no or low antibacterial activity, thus distinguishing them from other fluoroquinolnes which have highly potent antibacterial activity. These efflux pump inhibitory compounds have been shown to inhibit efflux pumps of different kinds present in gram-positive and gram-negative microbial strains.

Although the claimed compounds appear similar in structure to known antibacterial quinolones, they are relatively inactive bacterially (cf. below). Now for the first time they are shown and claimed to be effective EPIs.

The Examiner's statement that the method of inhibiting efflux pump is inherent in Miyake because the compounds are used to treat microbial infections is incorrect. As explained above and in the prior response, it is not correct that because a compound is active against resistant microbial strains, it is inherently also an EPIs.

Miyake teaches compounds that are useful as a prophylatic and/or therapeutic agentsfor peripheral arterial obstruction, acute myocardial infarction, or antitumor agents and as a prophylatic and/or therapeutic agent for osteoporosis.

Although in column 2, reference is made to WO93/13091 disclosing compounds with antibacterial activity, there is no suggestion that these compounds are efflux pump inhibitors or can be used with another antimicrobial agent. In fact, given the disclosure in column 1, lines 26-37 of Ledoussal of the possible mechanisms of antibacterials (inhibiting cell wall synthesis or repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting synthesis of nucleic acids), one skilled in the art would consider that the compounds do not have efflux pump activity.

Therefore, it is respectfully requested that the rejection be withdrawn.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

JANET I. CORD
LADAS & PARRY
26 West 61st. Street
New York, New York 10023
Reg. 33,778
Tel. (212) 708-1935